REMARKS

Claims 47-81 were pending in the application. Claims 47-81 were rejected. Claims 1-46 were previously canceled without prejudice to or disclaimer of the subject matter recited therein. Claims 47, 55, 60, 62, 64, and 67-76 are amended. Claims 82-84 are added. Claims 47-84 are now pending in the application. Claims 47, 67, and 82 are the independent claims. Reconsideration of the amended application is respectfully requested.

The examiner rejected claims 47, 50, 51, 55, 57, and 63 as being anticipated by USP 6,228,326 (Boxer et al.).

As amended, claim 47 recites a method for the electrophoretic separation of particles, particularly of membrane-adherent macromolecules. The method includes applying the particles to a substrate-supported membrane such that the particles are mobile across a surface of the substrate-supported membrane. An electrical field is provided that has a direction that is oriented along the surface across which the particles are mobile and electrophoresis is performed. The electrophoresis can be performed in one or more of the following two procedures. According to the first procedure, either the strength or the direction, or both, of the electrical field is temporarily modified such that a resulting force acts on the particles causing movement among the particles that depends on the length of the particles. According to the second procedure, a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface is used to provide a force acting on the moving particles that depends on the length of the particles.

In contrast, Boxer et al. disclose arrays of independently-addressable supported fluid bilayer membranes. In particular, with respect to applying particles to a membrane, Boxer et al. teach two cases: a) biomolecules integrated into the supported bilayer, and b) biomolecules attached to the supported bilayer. In the case of integrated biomolecules, these are part of the membrane and are attached within the membrane to lipid molecules forming the bilayer. Such biomolecules are "transmembrane molecules". Thus, there is no application of particles such that the particles are mobile across a surface of the membrane, as recited in claim 47. The examples disclosed by Boxer et al. in the context of attached biomolecules are always directed to a specific binding (key-lock mechanism). In other words, the biomolecule is bound (for example, by covalent attachment) to a specific binding partner within the membrane. Thus, a part of the overall molecule is also part of the membrane. Then, when a force is acting on the molecule, the overall molecule, that is, not only the part attached to the bilayer but also the binding partner within the membrane, is moving. There is no application of the particles to allow movement of the particles across the surface of the membrane as recited in claim 47.

The examiner cited the passage at column 13, lines 36-52 as disclosing application of molecules to the surface of an already-formed membrane. However, in that passage, Boxer et al. disclose linking biomolecules to a supported lipid bilayer via specific interactions between the side chain of the amino acid histidine and divalent transition metal ions immobilized on the membrane surface. Thus, this is a specific binding of the particles to the membrane, as described above, and not application of the

particles to the membrane such that the particles are mobile across a surface of the membrane, as recited in claim 47.

Further, the examiner acknowledged that Boxer et al. do not disclose modifying the strength or direction of an electric field to cause movement of the particles, as recited in claim 47, but correctly noted that these elements were optional. The other claimed option for performing electrophoresis is using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface that provides a force acting on the moving particles that depends on the length of the particles. The examiner asserted that Boxer et al. disclose using a structured substrate comprising ribs to support the membrane, citing Figures 1, 2, and 5.

Boxer et al. disclose a structured substrate that supports the membrane, but this substrate does not provide a force acting on the moving particles that depends on the length of the particles, as recited in claim 47. Rather, this structured substrate divides the membrane. As described at column 5, lines 44-49, the substrate surface shown in Fig. 1 includes a plurality of distinct bilayer-compatible surface regions 24 separated by one or more bilayer barrier regions 26. The bilayer barrier regions are preferably formed of a material 28 that is different than the material 22 forming the bilayer-compatible surface regions. As disclosed by Boxer et al., a separate bilayer expanse 30 is carried on each bilayer-compatible surface region 24. The material forming the bilayer barrier regions has intrinsic chemical/electrostatic properties that result in a hard barrier to the presence of the bilayer. See column 5, line 50 through column 6, line 17. Figure 4 shows a cross-section of a device fabricated from the support grid shown in Figure 1. As shown,

of bilayer-compatible material 54 are completely separated by bilayer barrier material 52. See column 8, lines 11-31. Thus, the substrate does not have a structured membrane-compatible surface that provides a force on moving particles mobile across the surface of the membrane. Rather, the Boxer et al. substrate includes structures formed of a different material that separate distinct areas of the membrane and act as absolute barriers to movement of particles within the membrane.

Similarly, claim 55 recites that the structured membrane-compatible surface includes ribs supporting the membrane. Boxer et al. do not disclose this feature. Rather, Boxer et al. disclose several bilayer-compatible surfaces interrupted by bilayer barrier regions. These barrier regions do not support the bilayer and do not form part of the bilayer-compatible surface.

In summary, Boxer et al. do not disclose applying particles to a substrate-supported membrane such that the particles are mobile across a surface of the substrate-supported membrane, as recited in claim 47. Further Boxer et al. do not disclose using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface that provides a force acting on the moving particles that depends on the length of the particles, or temporarily modifying the strength and/or direction of the electrical field, as recited in claim 47. In contrast, Boxer et al. disclose specifically binding the particles to a lipid bilayer, and providing a substrate having bilayer barrier structures interrupting the bilayer and preventing movement of particles at the barriers.

For at least the reasons noted above, Boxer et al. do not anticipate the invention recited in claim 47. Claims 50, 51, 55, 57, and 63 depend from claim 47, and therefore

also are not anticipated by Boxer et al. The rejection of claims 47, 50, 51, 55, 57, and 63, therefore, should be withdrawn.

The examiner rejected claim 48 as being obvious in view of Boxer et al., and further in view of USP 5,637,201 (Raguse et al.).

Claim 48 depends from claim 47. As noted above, Boxer et al. fail to disclose certain features recited in claim 47. For example, Boxer et al. do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Raguse et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. Because neither reference teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claim 48. The rejection of claim 48, therefore, should be withdrawn.

The examiner rejected claim 49 as being obvious in view of Boxer et al. and Raguse et al., and further in view of USP 5,552,155 (Bailey et al.).

Claim 49 depends from claim 47. As noted above, Boxer et al. and Raguse et al. fail to disclose a number of the features recited in claim 47. For example, Boxer et al. and Raguse et al. do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Bailey et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. and Raguse et al.

Because none of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claim 49. The rejection of claim 49, therefore, should be withdrawn.

The examiner also rejected claims 52-54 as being obvious in view of Boxer et al., and further in view of Allington et al.

Claims 52-54 depend from claim 47. As noted above, Boxer et al. fail to disclose a number of the features recited in claim 47. For example, Boxer et al. do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Allington et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. Because neither of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claims 52-54. The rejection of claims 52-54, therefore, should be withdrawn.

The examiner rejected claims 56 and 59 as obvious in view of Boxer et al., and further in view of Austin et al.

Claims 56 and 59 depend from claim 47. As noted above, Boxer et al. fail to disclose a number of the features recited in claim 47. For example, Boxer et al. do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-

compatible surface. Austin et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. Because neither of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claims 56 and 59. The rejection of claims 56 and 59, therefore, should be withdrawn.

The examiner rejected claims 58 and 64-66 as obvious in view of Boxer et al., and further in view of Wiktorowicz et al.

Claims 58 and 64-66 depend from claim 47. As noted above, Boxer et al. fail to disclose a number of the features recited in claim 47. For example, Boxer et al. do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Wiktorowicz et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. Because neither of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claims 58 and 64-66. The rejection of claims 58 and 64-66, therefore, should be withdrawn.

The examiner rejected claims 60 and 62 as obvious in view of Boxer et al., and further in view of Groves et al.

Claims 60 and 62 depend from claim 47. As noted above, Boxer et al. fail to disclose a number of the features recited in claim 47. For example, Boxer et al. do not disclose particles mobile across a surface of the substrate-supported membrane;

temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Groves et al. also do not disclose these features, and therefore do not overcome the deficiency of Boxer et al. Because neither of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claims 60 and 62. The rejection of claims 60 and 62, therefore, should be withdrawn.

The examiner rejected claim 61 as obvious in view of Boxer et al., and further in view of Groves et al. and Raguse et al.

Claim 61 depends from claim 47. As noted above, Boxer et al., Groves et al., and Raguse et al. all fail to disclose a number of the features recited in claim 47. For example, these references do not disclose particles mobile across a surface of the substrate-supported membrane; temporarily modifying the strength and/or direction of the electrical field; or using a substrate supporting the substrate-supported membrane that has a structured membrane-compatible surface. Because none of the references teaches or suggests all of these features, no combination of the teachings of these references could render obvious the invention recited in claim 61. The rejection of claim 61, therefore, should be withdrawn.

The examiner rejected claims 67-70, 72, and 75 as being anticipated by Stowell et al.

Independent claim 67 recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported

membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, Stowell et al. disclose sol-gel encapsulation of lipid membranes and proteins. In particular, Stowell et al. disclose the preparation of sandwiched LB lipid membranes, which are formed at the surface of a substrate. Water is removed from the sandwiched membrane, which is air dried. However, Stowell et al. do not disclose at least one channel having a bottom surface that includes a substrate-supported membrane. Because Stowell et al. do not disclose this element of claim 67, the claimed invention is not anticipated by the reference. Claims 68-70, 72, and 75 depend from claim 67, and therefore also are not anticipated by Stowell et al. The rejection of claims 67-70, 72, and 75, therefore, should be withdrawn.

The examiner rejected claims 67, 69, 70, 72, 73, and 75 as being anticipated by Peterson.

Independent claim 67 recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, Peterson discloses a biosensor including a lipid membrane containing gated ion channels. Peterson discloses a lipid bilayer 7 formed on a PTFE sheet 6. A porous gel is applied to the lipid membrane to protect the membrane from dehydration and physical damage. The biosensor can be packaged and stored in a dry state, for rehydration prior to use. However, Peterson does not disclose at least one channel having

a bottom surface that includes a substrate-supported membrane. Because Peterson does not disclose this element of claim 67, the claimed invention is not anticipated by the reference. Claims 69, 70, 72, 73, and 75 depend from claim 67, and therefore also are not anticipated by Peterson. The rejection of claims 67, 69, 70, 72, 73, and 75 therefore, should be withdrawn.

The examiner rejected claims 67, 69-72, 75-78, 80, and 81 as being unpatentable over Groves et al. in view of Goodrich, Jr. et al.

Independent claim 67 recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, Goodrich, Jr. et al. teach a method for freeze-drying of cells or cell-like materials. In particular, a cryoprotective composition is added to the cells in order to avoid formation of a "storage lesion" (column 1, lines 40-44). This problem occurs in the case of three-dimensional mechanically stable structures such as liposomes. However, there is no disclosure or suggestion by either Groves et al. or Goodrich et al. that such a freeze-drying would also work in the case of two-dimensional structures such as the planar supported bilayers disclosed by Groves et al. In particular, the planar bilayer disclosed by Groves et al. is used for electrophoresis. If a cryoprotective composition were to be added to the membrane as taught by Goodrich et al., the results of the electrophoresis would be modified. Thus, modifying the Groves et al. process by adding a cryoprotective composition and freeze-drying the resulting composition according to

the teachings of Goodrich et al. is problematic. This combination is not suggested in either reference, and one of skill in the art would recognize that further experimentation and inventive effort would be required to apply the combination of teachings in an effective manner for electrophoretic applications, if a successful result is even possible, which is not evident from the teachings of the references.

In view of the foregoing, it is submitted that combination of the teachings of the cited references in an effort to render obvious the invention recited in claim 67 is improper, as being unmotivated and possible unworkable. Claims 69-72, 75-78, 80, and 81 depend from claim 67, and therefore also are not rendered obvious by the cited references. The rejection of claims 67, 69-72, 75-78, 80, and 81, therefore, should be withdrawn.

The examiner rejected claims 67, 69, 70, and 72-80 as being unpatentable over Boxer et al., in view of Goodrich, Jr. et al.

Independent claim 67 recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, Goodrich, Jr. et al. teach a method for freeze-drying of cells or cell-like materials. In particular, a cryoprotective composition is added to the cells in order to avoid formation of a "storage lesion" (column 1, lines 40-44). This problem occurs in the case of three-dimensional mechanically stable structures such as liposomes. However, there is no disclosure or suggestion by either Boxer et al. or Goodrich et al. that such a

freeze-drying would also work in the case of two-dimensional structures such as the planar supported bilayers disclosed by Boxer et al. (column 7, lines 35-40; the examiner cited PMMA as the "support", but the PMMA is actually used by Boxer et al. as a photoresist, and is not present in the resulting substrate). In particular, the planar bilayer disclosed by Boxer et al., for applications relevant to the claimed invention, is used for electrophoresis, particularly for measuring receptor size and/or aggregation (column 19, lines 20-57). If a cryoprotective composition were to be added to the membrane as taught by Goodrich et al., the results of the electrophoresis would be modified. Thus, modifying the Boxer et al. process by adding a cryoprotective composition and freeze-drying the resulting composition according to the teachings of Goodrich et al. is problematic. This combination is not suggested in either reference, and one of skill in the art would recognize that further experimentation and inventive effort would be required to apply the combination of teachings in an effective manner for electrophoretic applications, if a successful result is even possible, which is not evident from the teachings of the references.

In view of the foregoing, it is submitted that combination of the teachings of the cited references in an effort to render obvious the invention recited in claim 67 is improper, as being unmotivated and possible unworkable. Claims 69, 70, and 72-80 depend from claim 67, and therefore also are not rendered obvious by the cited references. The rejection of claims 67, 69, 70, and 72-80, therefore, should be withdrawn.

The examiner rejected claim 68 as being unpatentable over Groves et al. and Goodrich, Jr. et al., in view of Bailey et al.

Claim 68 depends from claim 67, which recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, as noted above, Goodrich, Jr. et al. teach a method for freeze-drying of cells or cell-like materials. In particular, a cryoprotective composition is added to the cells in order to avoid formation of a "storage lesion" (column 1, lines 40-44). This problem occurs in the case of three-dimensional mechanically stable structures such as liposomes. However, there is no disclosure or suggestion by either Groves et al. or Goodrich et al. that such a freeze-drying would also work in the case of two-dimensional structures such as the planar supported bilayers disclosed by Groves et al. In particular, the planar bilayer disclosed by Groves et al. is used for electrophoresis. If a cryoprotective composition were to be added to the membrane as taught by Goodrich et al., the results of the electrophoresis would be modified. Thus, modifying the Groves et al. process by adding a cryoprotective composition and freeze-drying the resulting composition according to the teachings of Goodrich et al. is problematic. This combination is not suggested in either reference, and one of skill in the art would recognize that further experimentation and inventive effort would be required to apply the combination of teachings in an effective manner for electrophoretic applications, if a successful result is even possible, which is not evident from the teachings of the

references. Bailey et al., which is only relied on for the disclosure of bilayers including cationic lipids, does not provide the necessary motivation or missing teaching required to overcome the noted efficiency.

In view of the foregoing, it is submitted that combination of the teachings of the cited references in an effort to render obvious the invention recited in claim 67 is improper, as being unmotivated and possible unworkable. Claim 68 depends from claim 67, and therefore also is not rendered obvious by the cited references. The rejection of claim 68, therefore, should be withdrawn.

The examiner rejected claim 68 as being unpatentable over Boxer et al. and Goodrich, Jr. et al., in view of Bailey et al.

Claim 68 depends from claim 67, which recites a microchannel electrophoresis chamber, including at least one channel having a bottom surface that includes a substrate-supported membrane. The substrate-supported membrane includes a substrate and a fluid lipid membrane, wherein the fluid lipid membrane is dried up.

In contrast, as noted above, Goodrich, Jr. et al. teach a method for freeze-drying of cells or cell-like materials. In particular, a cryoprotective composition is added to the cells in order to avoid formation of a "storage lesion" (column 1, lines 40-44). This problem occurs in the case of three-dimensional mechanically stable structures such as liposomes. However, there is no disclosure or suggestion by either Boxer et al. or Goodrich et al. that such a freeze-drying would also work in the case of two-dimensional structures such as the planar supported bilayers disclosed by Boxer et al. (column 7, lines 35-40; the examiner cited PMMA as the "support", but the PMMA is actually used by

Boxer et al. as a photoresist, and is not present in the resulting substrate). In particular, the planar bilayer disclosed by Boxer et al., for applications relevant to the claimed invention, is used for electrophoresis, particularly for measuring receptor size and/or aggregation (column 19, lines 20-57). If a cryoprotective composition were to be added to the membrane as taught by Goodrich et al., the results of the electrophoresis would be modified. Thus, modifying the Boxer et al. process by adding a cryoprotective composition and freeze-drying the resulting composition according to the teachings of Goodrich et al. is problematic. This combination is not suggested in either reference, and one of skill in the art would recognize that further experimentation and inventive effort would be required to apply the combination of teachings in an effective manner for electrophoretic applications, if a successful result is even possible, which is not evident from the teachings of the references.

Bailey et al., which is only relied on for the disclosure of bilayers including cationic lipids, does not provide the necessary motivation or missing teaching required to overcome the noted efficiency. Further, Boxer et al. teach the specific binding of particles to the membrane, that is, the particles are electrostatically bound to a specific binding partner within the membrane. Bailey et al. utilize a cationic fluid lipid membrane, which makes it clear that there is no electrostatic binding and no specific binding, and therefore Bailey et al. teach away from using a combination of the teachings of the references as incompatible, which would be recognized by one of ordinary skill in the art.

In view of the foregoing, it is submitted that combination of the teachings of the cited references in an effort to render obvious the invention recited in claim 67 is improper, as being unmotivated and possible unworkable. Claim 68 depends from claim 67, and therefore also is not rendered obvious by the cited references. The rejection of claim 68, therefore, should be withdrawn.

Claims 82-84 are added to recite additional aspects of the invention. Claim 82 explicitly recites the non-specific binding of particles to the substrate-supported membrane, which is a cationic fluid lipid membrane. For at least the reasons noted above, it is submitted that at least these claimed features render this claim allowable. Further, claims 83 and 84 recite separately the electrophoretic processes of modifying the strength and/or direction of the electrical field, and using a structured substrate to provide a force on moving particles, respectively.

Based on the foregoing, it is submitted that all rejections have been overcome. It is therefore requested that the Amendment be entered, the claims allowed, and the case passed to issue.

Respectfully submitted,

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